

CLINICAL PRACTICE

# Causation of term perinatal hypoxic-ischaemic basal ganglia and thalamus injury in the context of cerebral palsy litigation: Position statement

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Basal ganglia and thalamus (BGT) hypoxic-ischaemic brain injury is currently the most contentious issue in cerebral palsy (CP) litigation in South Africa (SA), and merits a consensus response based on the current available international literature. BGT pattern injury is strongly associated with a preceding perinatal sentinel event (PSE), which has a sudden onset and is typically unforeseen and unpreventable. Antepartum pathologies may result in fetal priming, leading to vulnerability to BGT injury by relatively mild hypoxic insults. BGT injury may uncommonly follow a gradual-onset fetal heart rate deterioration pattern, of duration  $\geq 1$  hour. To prevent BGT injury in a clinical setting, the interval from onset of PSE to delivery must be short, as little as 10 - 20 minutes. This is difficult to achieve in any circumstances in SA. Each case needs holistic, multidisciplinary, unbiased review of all available antepartum, intrapartum and postpartum and childhood information, aiming at fair resolution without waste of time and resources.

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Basal ganglia and thalamus (BGT) hypoxaemic ischaemic injury is observed on magnetic resonance imaging in the CP-affected child. It usually involves not only the BGT, but also a cluster of structures including the perirolandic cortex, giving a BGT-pattern injury. The tissues in this cluster are highly metabolically active, and thus vulnerable at term to sudden-onset severe ischaemia, where the brain has insufficient time to autoregulate and redirect blood flow.<sup>[1]</sup> In the context of hypoxia-ischaemia, BGT pattern injury has been termed 'acute profound', reflecting the suddenness and severity of the insult. A less severe insult, with a 'prolonged partial' injury, involves gradual-onset ischaemia that damages the cortical watershed areas, sparing the BGT.<sup>[1,2]</sup> With acute profound asphyxia, BGT injury may occur in as little as 10 minutes from onset of the acute insult, allowing no time for effective obstetric intervention.

Human case series have shown a strong association between BGT pattern injury and sudden-onset hypoxic-ischaemic events, known as perinatal sentinel events (PSEs).<sup>[3-8]</sup> PSEs include not only clinically obvious placental abruption, cord prolapse and uterine rupture, but also 'concealed' events presenting as sudden-onset fetal bradycardia of uncertain origin, possibly the result of acute umbilical cord compression.<sup>[7,8]</sup> There is no reason to believe that brain injury pathogenesis differs between clinically obvious PSEs and those of uncertain origin. In both scenarios, the fetal heart rate (FHR) signature is acute-onset sustained fetal bradycardia. Typically, PSEs are not foreseeable, although some, for example placental abruption and uterine rupture, can be foreseen and prevented in certain

circumstances.<sup>[10]</sup> A large proportion of BGT injuries follow PSEs that are not clinically obvious. For example, 5 out of 11 in the series of Pasternak and Gorey<sup>[5]</sup> had no apparent cause, as with both cases of Okumura *et al.*,<sup>[6]</sup> and at least 4 of 16 cases reported by Roland *et al.*<sup>[4]</sup> The BGT injury pattern is rarely seen in the absence of a PSE. Sie *et al.*<sup>[7]</sup> noted that only 1 of 18 children with BGT pattern injury did not have a history of 'acute and profound asphyxia'.<sup>[7]</sup> Pasternak and Gorey<sup>[5]</sup> observed that BGT lesions 'with relative or complete sparing of the remainder of the cerebral hemispheres have only occurred in infants whose fetal heart rate pattern or clinical circumstances suggested an acute and severe insult'.<sup>[5]</sup>

These and another source<sup>[11]</sup> established a successful defendant expert viewpoint in South African (SA) courts in the late 2010s that BGT pattern injury evolves so rapidly as to make it unpreventable in a clinical setting. Even in the presence of substandard obstetric care, defendants (provincial health departments) could not then be liable for the resultant CP.<sup>[12,13]</sup> Lawyers representing plaintiffs, and their experts, countered by pointing out limitations in the case series mentioned above. For example, Pasternak and Gorey's<sup>[5]</sup> series has been criticised for its conclusions on causation,<sup>[14]</sup> and the cardiotocographs (CTGs) of the two cases of Okumura *et al.*<sup>[6]</sup> raised doubts on the fetal pre-event status. Plaintiff experts also referred to animal research that implied an alternative pathogenesis in BGT injury. Fetal sheep exposed to repeated bouts of severe hypoxia developed lesions in the striata (basal ganglia), suggestive that a single severe insult is not the only plausible cause of such injury.<sup>[15,16]</sup>

In further support of their opinions, plaintiff experts cited Volpe's<sup>[17]</sup> textbook on newborn neurology, and guidelines of the American College of Obstetricians and Gynecologists (ACOG).<sup>[18]</sup> Both sources use the term 'cerebral-deep nuclear neuronal injury' to refer to BGT injury involving the perirolandic cortex, with ACOG appearing to follow Volpe's teachings. ACOG states that the cerebral-deep nuclear injury is the result of 'severe partial insult of prolonged duration or a combined partial with profound terminal insult'. The words 'partial' and 'prolonged' confusingly suggest that a prolonged partial insult is a cause of BGT pattern injury, contradicting the terminology introduced in our first paragraph. Yet ACOG then characterises the cerebral-deep nuclear injury as 'recognised most commonly after an acute near-total hypoxic-ischemic insult', the same terminology that Pasternak and Gorey<sup>[5]</sup> use to describe PSEs in their series.

The early 2020s have seen several new scientific contributions. Smith *et al.*<sup>[19]</sup> reported on 10 SA children who were subjects of medicolegal claims. All had cerebral palsy (CP) with BGT pattern injury, with no obvious preceding PSE. Eight had 'pathological' CTGs for durations >160 minutes before birth, implying that prolonged and gradual deterioration is usual in the absence of an obvious PSE. The article has been criticised for its literature interpretation, methodology and lack of transparency.<sup>[20]</sup> The authors did not provide reproduced CTG tracings with their article, or with their reply to critical correspondence.<sup>[21]</sup>

Plaintiff experts now frequently refer to a narrative review on neuroimaging in neonatal encephalopathy by Wisnowski *et al.*<sup>[22]</sup> The review briefly mentions causation of BGT pattern injury, echoing the opinions of Volpe and ACOG, as summarised above. The authors cite two animal studies, one of which found that fetal monkeys sustained BGT injuries after repeated insults in combination with a single severe hypoxic-ischaemic event.<sup>[23]</sup> But the single severe intrauterine event in the animals preceded the repeated insults, which were induced *after* birth during neonatal care. This cannot support ACOG's suggestion that BGT pattern injury results from intrapartum 'partial insult' with later 'profound terminal insult'.

Baxter<sup>[24]</sup> reviewed data from multiple studies on outcomes after 'sentinel events' (defined by implication as clinically obvious) and 'fetal monitoring' (where there was acute bradycardia with no obvious event). He notes the strong association between BGT pattern injury and acute severe hypoxic-ischaemic insult. His data show that isolated BGT injury can occur after just 10 minutes of bradycardia, but generally within 20 minutes. He observes that added injury in the perirolandic cortex can occur after 15 minutes of bradycardia, with further cortical involvement beyond the BGT cluster requiring a duration >30 - 40 minutes. Baxter states that these data do 'not strongly support' the suggestion in Volpe *et al.*<sup>[25]</sup> that perirolandic cortex injury represents a more chronic partial type of insult. Baxter concedes the 'difficulties in answering the question whether earlier intervention could have prevented brain injury' and recommends specific research to fill these knowledge gaps.

Nakao *et al.*<sup>[26]</sup> analysed FHR patterns in 1 069 Japanese children with severe CP born at  $\geq 34$  weeks' gestation. In 167 children, a 'reassuring-prolonged deceleration' (R-PD) pattern developed abruptly on CTG 'usually within a few minutes' from a normal FHR to prolonged deceleration or bradycardia just before delivery. This is typical of a PSE. In 93 cases (56%), there was no apparent cause, 30 (18%) had umbilical cord abnormalities detectable only postpartum and only a minority ( $n=53$ ; 32%) followed clinically obvious PSEs. In answer to Baxter, Nakao *et al.*<sup>[27]</sup> followed up with data on a subset of this cohort ( $n=672$ ), in which magnetic resonance imaging (MRI) could be correlated with FHR patterns. Isolated BGT injury, and BGT injury with added injury in one or two regions of the cortex (indicating

added perirolandic cortex involvement) occurred twice as frequently with the R-PD pattern as with Hon's pattern<sup>[27]</sup> of gradual FHR deterioration. This confirms the association between BGT pattern injury and PSE, irrespective of perirolandic cortex involvement. It also shows that Hon's pattern, which usually evolves over  $\geq 1$  hour, can uncommonly precede BGT injury. The authors also found that persistently non-reactive FHR patterns or bradycardia were present on hospital admission in over one-third of children with BGT pattern injury where there was a classifiable CTG.<sup>[27]</sup> A persistently non-reactive CTG or bradycardia on admission is suggestive of an event developing antepartum or before the mother accesses obstetric care. The authors further showed significant contributions from umbilical cord abnormalities, intrauterine infection, fetal growth restriction and fetomaternal transfusion. This lends support to concerns that these pathologies and placental disorders may prime the fetus antepartum to be predisposed to later brain injury from a relatively mild hypoxic-ischaemic insult.<sup>[27-30]</sup> Another study performed in Pretoria, SA, using continuous-wave Doppler ultrasound in a low-risk population (Umbiflow) revealed that the prevalence of absent end diastolic flow (AEDF) was 10 $\times$  higher than previously recorded,<sup>[31]</sup> reinforcing the notion that there are primed fetuses for hypoxia that sometimes enter the intrapartum undetected, and that minor hypoxic episodes create a vulnerability to BGT injury.

This summary of the current state of knowledge on causation of BGT pattern injury forms the foundation of our position statement. The statement should serve primarily as information for obstetricians engaged as experts in CP litigation.

## Position statement

1. BGT pattern injury is strongly associated with a preceding PSE, which has a sudden onset and is typically unforeseen and unpreventable. PSEs may be clinically obvious or detectable only on continuous FHR monitoring (concealed). The injury pathogenesis does not differ between clinically obvious and concealed PSEs.
2. A PSE may occur and cause BGT injury before labour or before maternal admission to hospital.
3. Antepartum pathologies may result in fetal priming, leading to vulnerability to BGT injury by relatively mild hypoxic insults.
4. BGT injury may uncommonly follow a gradual-onset FHR deterioration pattern, of duration  $\geq 1$  hour.
5. To prevent BGT injury in a clinical setting, the interval from onset of PSE to delivery must be short, as little as 10 - 20 minutes. This is difficult to achieve in any circumstances in SA.
6. Isolated BGT injury and BGT pattern injury with involvement of the perirolandic cortex are equally strongly associated with preceding PSEs.
7. Some PSEs, for example placental abruption or uterine rupture, can be foreseen and prevented in certain situations. Preventable causes can be managed, e.g. overstimulation, and if fully dilated, engaged instrumental delivery can be attempted. Thus good intrapartum care is crucial.
8. Each case needs holistic, multidisciplinary, unbiased review of all available antepartum, intrapartum and postpartum and childhood information, aiming at fair resolution without waste of time and resources.<sup>[32]</sup>

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analysis, manuscript writing/editing. KF: protocol/project development, management data analysis, manuscript writing/editing. PS-P: protocol/project development, management data analysis, manuscript writing/editing. EM: protocol/project development, management, data analysis, manuscript writing/editing. LP: protocol/project development, management, data analysis, manuscript writing/editing. IS: protocol/project development, management, data analysis, manuscript writing/editing.

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